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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/532,868	04/28/2005	Francois Andre	03715.0147	3789
22852	7590	07/09/2008	EXAMINER	
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP 901 NEW YORK AVENUE, NW WASHINGTON, DC 20001-4413			RIGGS II, LARRY D	
		ART UNIT	PAPER NUMBER	
		1631		
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/532,868	ANDRE ET AL.	
	Examiner	Art Unit	
	LARRY D. RIGGS II	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 11 March 2008.
 2a) This action is **FINAL**. 2b) This action is non-final.
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 27-30 and 33-39 is/are pending in the application.
 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
 5) Claim(s) _____ is/are allowed.
 6) Claim(s) 27-30 and 33-39 is/are rejected.
 7) Claim(s) _____ is/are objected to.
 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.
 10) The drawing(s) filed on 11 March 2008 is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413)
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	Paper No(s)/Mail Date. _____ .
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)	5) <input type="checkbox"/> Notice of Informal Patent Application
Paper No(s)/Mail Date _____.	6) <input type="checkbox"/> Other: _____ .

DETAILED ACTION

Applicant's amendments filed 11 March 2008 are acknowledged and entered.

Status of Claims

Cancellation of claims 1-26, 31, 32 and 40-67 are acknowledged. Claims 27-30 and 33-39 are currently pending and under consideration.

Withdrawn Rejections/Objections

The objection of the disclosure in the Office action mailed 11 October 2007 is withdrawn in view of the amendments filed 11 March 2008.

The objection to claim 37 in the Office action mailed 11 October 2007 is withdrawn in view of the amendments filed 11 March 2008.

Sequence Rules Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2).

Patent applications which contain disclosures of nucleotide and/or amino acid sequences must contain, as a separate part of the disclosure, a paper or compact disc copy (see § 1.52(e)) disclosing the nucleotide and/or amino acid sequences and associated information using the symbols and format in accordance with the requirements of §§ 1.822 and 1.823. This paper or compact disc copy is referred to elsewhere in this subpart as the "Sequence Listing." Each sequence disclosed must appear separately in the "Sequence Listing."

Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph

(c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

A copy of the "Sequence Listing" referred to in paragraph (c) of this section must also be submitted in computer readable form (CRF) in accordance with the requirements of § 1.824.

In addition to the paper or compact disc copy required by paragraph (c) of this section and the computer readable form required by paragraph (e) of this section, a statement that the "Sequence Listing" content of the paper or compact disc copy and the computer readable copy are the same must be submitted with the computer readable form, e.g., a statement that "the sequence listing information recorded in computer readable form is identical to the written (on paper or compact disc) sequence listing."

In the instant case, the specification, (page 21), disclosed amino acid sequences greater than 4 bases in length not followed by a sequence identifier (SEQ ID NO:X).

Applicants are given the same response time regarding this failure to comply as that set forth to respond to this office action. Applicants are reminded that it is required that SEQ ID Nos be amended into the specification at each sequence, and that when a sequence is presented in a drawing regardless of the format or the manner of presentation of that sequence in the drawing, the sequence must still be included in the Sequence Listing and the sequence identifier ("SEQ ID NO:X") must be used, either in the drawing or in the Brief Description of the Drawings. Failure to comply with these requirements may result in ABANDONMENT of the application under 37 CFR 1.821(g).

Appropriate correction is required.

Claim Suggestions

Claim 27, line 3, Examiner suggests placing a colon at the end of “comprising the steps of”.

Claims 27, 28, 30 and 33-35 have multiple periods throughout the claims. Examiner suggests replacing periods with parentheses.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 27-30 and 33-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 27 recites numerous steps starting with the letter (j) in 4. The metes and bounds of the limitations are unclear as to where the previous steps (a-i) are or how they pertain to recited steps (j-s).

Claim 27 recites the limitation “docking of a substrate on an enzyme, a 3-D structure of which is available” in line 2. The metes and bounds of the limitation are unclear whether the 3-D structure is available for the substrate, the enzyme or the combination of substrate docked with the enzyme.

Claim 27 recites the limitation “the other atoms” and “the mobile atoms” in line 3 of step (k). There is insufficient antecedent basis for this limitation in the claim.

Claim 27 recites the limitation “the structure of the protein” in line 2 of step (l). There is no clear antecedent basis for this limitation in the claim. A substrate and an

enzyme are previously recited in the claim and it is unclear what the limitation pertains

to

Deleted:

Claim 27 recites the limitation "the atoms" in line 2 of step (m) and line 3 of step (o). There is no clear antecedent basis for this limitation in the claim because "some atoms", "the other atoms" or "the mobile atoms" are recited previously in the claim, thus it is unclear what atoms are referred to by "the atoms."

Claim 27 recites the limitation "the protein" in line 2 of step (m). There is no clear antecedent basis for this limitation in the claim because a substrate and an enzyme are previously recited in the claim and it is unclear what the limitation pertains to.

Claim 27 recites the limitation "the potential energy" in line 1 of step (ii) following step (m). There is no clear antecedent basis for this limitation in the claim because "the potential energy (Ep)", "the potential energy", "other Ep minima" and "(Ep)" have been recited previously in the claim.

Claim 28 recites the limitation "the backbone atoms N-Ca-CO" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 28 recites the limitation "Coc" in line 2. The metes and bounds of the limitation are unclear. Neither the claim nor the specification provides a clear and precise definition of the limitation and one skilled in the art would be unclear to what the limitation pertains.

Claim 30 recites the limitation "forces linked to a. the distance between atoms, b. the angles of valence, c. the dihedral angles, d. the deformation with regard to planar geometry, e. the electrostatic field, f. the Vander Waals forces, g." in lines 2-4. The

metes and bounds of the limitation are unclear what "a", "b", "c", "d", "e", "f" and "g" refer. The previous claims do not recite "a", "b", "c", "d", "e", "f" and "g" or any steps labeled "a", "b", "c", "d", "e", "f" and "g".

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 27-30 and 33-39 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The claims are drawn to a computer-assisted method for performing restrained dynamics docking of a substrate on an enzyme, wherein a 3-D structure is available.

Since the claimed invention involves mathematical algorithm, which is a judicial exception, the following analysis of facts of this particular patent application follows the rationale suggested in the "Interim Guidelines for Examination of Patent Applications for Patent Subject Matter Eligibility" (OG Notices: 22 November 2005, available from the US PTO website at

<http://www.uspto.gov/web/offices/com/sol/og/2005/week47/og200547.htm>).

The Guidelines states:

To satisfy section 101 requirements, the claim must be for a practical application of the § 101 judicial exception, which can be identified in various ways (Guidelines, p. 19):

- *The claimed invention "transforms" an article or physical object to a different state or thing.*

- The claimed invention otherwise produces a useful, concrete and tangible result.

In the instant claims, there is no physical transformation by the claimed invention because all steps include determining and simulating parameters around docking a substrate to an enzyme, thus the Examiner must determine if the instant claims produce a useful, tangible, and concrete final result.

In determining if the instant claims have a useful, tangible, and concrete final result, the Examiner must determine each standard individually. For a claim to be “useful”, the claim must produce a final result that is specific, substantial and credible. For a claim to be “tangible”, the claim must set forth a practical application of the invention that produces a real-world final result. For a claim to be “concrete”, the process must have a final result that can be substantially repeatable or the process must substantially produce the same result again. Furthermore, the claim must recite a useful, tangible, and concrete final result in the claim itself, and the claim must be limited only to statutory embodiments. Thus if the claim is broader than the statutory embodiments of the claim, the Examiner must reject the claim as non-statutory.

Method claims 27-30 and 33-39 do not produce a tangible final result. A tangible requirement requires that the claim must set forth a practical application of the questionnaire and scoring of answers, to produce a real-world result. The instant claims are drawn to a method of performing docking of a substrate on an enzyme. However, the last step of the claims includes generating a result in a user readable format. This is not a tangible final result. The result is generated into a particular format, however,

there is no guarantee that the user will have access to said result, despite what type of format the result is in.

Since the claim itself must include a useful, concrete and tangible final result, the instant claims are non-statutory.

This rejection could be overcome by amendment of the claims to recite that a specific final result of the process is outputted to a user, or by including a result that is a physical transformation. The applicants are cautioned against introduction of new matter in an amendment.

Response to Arguments

Applicant's arguments filed 11 March 2008 have been fully considered but they are not persuasive.

Applicant's argue that a final step added to claim 27, from which all pending claims directly or indirectly depend, recite that a result is generated in a user readable format, as the Examiner suggested in the Office Action mailed October 11, 2007 and accordingly ask that the rejection be withdrawn.

Applicant's arguments are not persuasive.

The Office Action mailed October 11, 2007 provided "this rejection could be overcome by amendment of the claims to recite that a result of the process is outputted to a display, or to a user, or in a graphical format, or in a user readable format, or by including a result that is a physical transformation."

Applicants only generated a result in a user readable format. This is not outputting a result to a user. There is no guarantee that a user will have access to the

generated result in the user readable format. Generating a result is not outputting a result.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 27, 28 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al., (Biochemistry, 2000, 39, 2484-2498) in view of Di Nola et al. (Proteins: Structure, Function, and Genetics, 1994, 19, 174-182) and further in view of Mager (Molecular Simulation, 1997, 19, 17-41).

The instant claim 27 provides a computer-assisted method for performing restrained dynamics docking of a substrate on an enzyme, a 3-D structure of which is available, comprising the steps of

- j. determining a force field, and independently simulating the presence of said enzyme in said force field,
- k. minimizing the potential energy (E_p) linked to said force field of said 3-D structure, wherein the spatial position of some atoms of said enzyme is fixed, and wherein the other atoms are mobile, by allowing mobility of the mobile atoms, by
 - i. simulating an increase in temperature (in order to give kinetic energy),
 - ii. and minimizing the potential energy by re-specifying the temperature as 0 Kelvin (K),
 - l. optionally repeating step k in order to obtain other E_p minima, wherein said E_p minima are such that the structure of the protein remains folded,
- m. minimizing E_p in said force field of said 3-D structure, wherein all the atoms of the protein are mobile, by
 - i. simulating an increase in temperature (in order to give kinetic energy), and

ii. minimizing the potential energy by re-specifying the temperature as

0 Kelvin (K),

n. simulating, at 0 K the presence of said substrate next to said enzyme,

o. optionally generating a molecular dynamics simulation on said substrate and enzyme (simulating an increase in temperature, in order to allow mobility of the atoms),

p. generating some constraints to said substrate, in order to impose that said substrate has interaction with said enzyme, wherein said constraints are final distance constraints between some atoms of said substrate and some atoms of amino-acids present in said active site,

q. generating a molecular dynamics simulation on said substrate and enzyme, with said constraints imposed in step p,

r. optionally, generating a molecular dynamics simulation on said substrate and enzyme without said constraints of step p; and

s. generating a result in a user readable format.

Chang et al. shows previously available P450 3-D structures to base the CYP119 structure on, (page 2485, right column, third paragraph), and simulating the CYP119 structure in a force field using the software AMBER, (page 2486, left column, fourth paragraph). Chang et al. shows unconstrained full protein minimization using a nonbonding cutoff of 8 Angstroms and a distance-dependent radial dielectric performed (final distance), with all residues, structural water molecules and the resting state heme

unit allowed to move in the minimization using combined steepest descent and conjugate gradient method (minimizing Ep) to obtain the fully minimized model, (page 2486, left column, last paragraph). Chang et al. shows protein-protein docking using program GRAMM, using substrates Putidaredoxin and FMN domain of CYP102 for the prediction of complex formation with CYP119, (page 2495, right column, first and second paragraphs). Chang et al. shows final distant constraints between CYP119 and Putidaredoxin and the FMN domain of P450BM3, (Table 7).

Chang et al. does not show simulating at zero Kelvin or generating a molecular dynamics simulation with a substrate and enzyme.

Di Nola et al. shows a method of molecular dynamics (MD) docking with a manipulation of temperature, using GROMOS87 and adapted to perform separate scaling of temperature for receptor, com (center of mass) of substrate, and internal degrees of freedom of the substrate, (page 175, left column, third paragraph – right column; page 176, left column, fifth paragraph). Di Nola et al. shows the phosphocholine-immunoglobulin complex was first energy-refined by 10ps of MD simulation at T=300 K followed by a 10 ps annealing of the temperature down to 10 K, (page 176, left column, last paragraph). Di Nola et al. shows that the docking simulation was performed by taking into account all atoms of the receptor included in a sphere of 2.0nm radius, centered at the com of the substrate in the crystal structure, with a cutoff radius of 0.8nm used for intermolecular interactions, (page 176, left column, last paragraph – right column, first paragraph; Figure 3)

Chang et al. and Di Nola et al. do not show simulating at zero Kelvin.

Mager shows geometry optimization and displays of protein structure using AMBER software with isothermal-isobaric conditions at 0 Kelvin temperature, (page 20, first paragraph; Figures 2 and 4-11).

Regarding claim 28, Chang et al. shows constrained energy minimization of both the backbone and side chains of nonstructurally conserved regions performed by AMBER, (page 2486, left column), then a number and duration of segments of constrained MD simulations increased, (2486, right column, second paragraph-last paragraph).

Regarding claim 35, Chang et al. shows simulation at 300 Kelvin, (abstract).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the homology modeling, molecular dynamic simulation of CYP119 and substrates by Chang et al. with the molecular dynamics simulation of the docking of substrates to proteins by Di Nola et al. and the simulations with zero Kelvin by Mager because Chang et al. shows reducing temperature to obtain a fully minimized model, (2486, left column, last paragraph).

Claim 30 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al., (Biochemistry, 2000, 39, 2484-2498) in view of Di Nola et al. (Proteins: Structure, Function, and Genetics, 1994, 19, 174-182) and further in view of Mager (Molecular Simulation, 1997, 19, 17-41) as applied to claims 27, 28 and 35 above, further in view of Case et al., AMBER User's Manual, April 20, 2002.

The instant claim 30 depends from claim 27 with the extra limitation that wherein said force field in step j comprises forces linked to the distance between atoms, angles of valence, dihedral angles, deformation with regard to planar geometry, electrostatic field, Van der Waals forces and hydrogen bonds.

Chang et al., Di Nola et al. and Mager are applied to claims 27, 28 and 35 above.

Chang et al., Di Nola et al. and Mager do not show force field in step j comprises forces linked to the distance between atoms, angles of valence, dihedral angles, deformation with regard to planar geometry, electrostatic field, Van der Waals forces and hydrogen bonds.

Case et al. shows force field linked to distance between atoms, angles of valence, dihedral angles, deformation with regard to planar geometry, electrostatic field, Van der Waals forces and hydrogen bonds with the Sander module that carries out energy minimization, molecular dynamics and NMR refinements and assessing improper torsions, (pages 80 and 294).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the homology modeling, molecular dynamic simulation of CYP119 and substrates by Chang et al. with the molecular dynamics simulation of the docking of substrates to proteins by Di Nola et al., the simulations with zero Kelvin by Mager and the force field linked to various angles, fields and forces of Case et al., because Chang et al. shows using AMBER software for molecular dynamic simulation (2486, left column, fourth paragraph).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LARRY D. RIGGS II whose telephone number is (571)270-3062. The examiner can normally be reached on Monday-Thursday, 7:30AM-5:00PM, ALT. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on 571-272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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